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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,148	YOSHIHARA, YOSHIHIRO	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the First Action on the Merits filed on January 28, 2005 is acknowledged.

Claims 1-4 have been amended. Claim 5 has been canceled. Claims 6-20 are newly added.

Claims 1-4, 6-20 are under consideration.

Priority

This application is claiming the benefit of a prior filed nonprovisional application under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required.

The instant application is a continuing application of 09/763,117. However, the instant application was not filed before the abandonment date of April 15, 2003. Accordingly, the instant application cannot claim priority to 09/763,117. The priority date of the instant application is the filing date of the application: July 14, 2003.

Information Disclosure Statement

With regards to the Applicant's comment regarding cited documents, wherein on Form PTO-1449, filed January 7, 2002, the Examiner has lined through the references and indicated references AI, AJ, AN as duplicates, the Applicant queries whether or not the Examiner has considered these references. In response, the Examiner has considered the references for the pending application.

Withdrawn Objections and Rejections

Drawings

Objection regarding the drawings has been withdrawn. Applicant has provided replacement drawings.

35 U.S.C §101

Rejection under 35 U.S.C.§ 101 has been withdrawn. Applicant has amended the claims.

35 U.S.C. §112, first paragraph, written description

Rejection under 35 U.S.C. § 112, first paragraph, written description, is withdrawn. Applicant has amended the claims. Further, the rejection regarding claims 1-3 were made in error and the rejection regarding claims 1-3 is withdrawn.

35 U.S. C. § 112, second paragraph

Rejection under 35 U.S.C. § 112, second paragraph, is withdrawn. Applicant has amended the claims.

35 U.S.C. § 102(b)

Rejection under 35 U.S.C. § 102(b) is withdrawn. Applicant has canceled the claim.

Maintained and New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) a transgenic mouse comprising a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a L7 promoter, wherein said transgenic mouse expresses the trans-synaptic tracer protein in Purkinje cells, and a transgenic mouse comprising a nucleic acid sequence encoding the trans-synaptic tracer protein operably linked to an OMP promoter, wherein said transgenic mouse expresses a trans-synaptic tracer protein in the olfactory or vomeronasal nerves,

2) a Purkinje cell obtained from the transgenic mouse comprising a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a L7 promoter, wherein said transgenic mouse expresses the trans-synaptic tracer protein in Purkinje cells and a cell from the olfactory or vomeronasal nerve obtained from the transgenic mouse comprising a nucleic acid sequence encoding the trans-synaptic tracer protein operably linked to an OMP promoter, wherein said transgenic mouse expresses a trans-synaptic tracer protein in the olfactory or vomeronasal nerves,

3) a method for using a Purkinje cell, or a cell from the olfactory or vomeronasal nerve in a screen for substances that alters the expression level of the trans-synaptic tracer protein,

does not reasonably provide enablement for:

1) any transgenic non-human animal comprising a transgene construct comprised of a nucleic acid encoding a trans-synaptic tracer protein operably linked to any neural promoter, wherein the transgenic non-human animal expresses trans-synaptic tracer protein in any neural cell,

2) any neuron obtained from said transgenic non-human animal,

3) a method of using said neuron in a screen for substances that alters the expression level of the trans-synaptic tracer protein,

3) a transgenic non-human neurological animal model obtained by crossing any transgenic non-human animal comprising a transgene construct comprised of a nucleic acid encoding a trans-synaptic tracer protein operably linked to any promoter with any non-human animal model of neurological disease,

4) a method for using said non-human neurological animal model in a screen for substances that restore or form compensatory neurological pathways.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for reasons of record stated in the First Office Action, dated September 9, 2004.

The claimed invention is to a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter, a method for screening substances having an effect upon cultured neurons obtained from said transgenic non-human animal, a cultured neuron obtained from said transgenic non-human animal, a transgenic non-human neural animal model obtained by crossing a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter to a non-human animal model for disease resulting from abnormal neural pathways or with a spontaneously mutated non-human animal model, and a method of using said transgenic non-human neurological animal model in a screen for substances.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Response to Arguments

Applicant's arguments filed January 28, 2005 have been fully considered but they are not persuasive.

With regards to "trans-synaptic tracer protein," the Examiner finds the Applicant's argument persuasive under the following situations. The Applicant has demonstrated different types of "trans-synaptic tracer" proteins which have been used in prior art studies. These include the C-terminal fragment of tetanus neurotoxin, wheat germ agglutinin (WGA), barley lectin (BL) (Applicant's Response, page 10, parag. 3, page 11, parag. 3). For this reason, the Examiner finds the broad scope of "trans-synaptic tracer" protein enabled. With regards to using these trans-synaptic tracer proteins in a variety of non-human animals the Applicant has pointed to art which has used trans-synaptic tracer proteins in a wide variety of non-human animals: bird, rabbits, cats, mice, monkeys (Applicant's Response, page 10, 4th parag.), and fly (Yoshihara et al., 1999, Neuron, 22: 33-41). For this reason, the Examiner finds the use of trans-synaptic tracer proteins in different species of non-human animals enabling.

However, with regards to the issue of the broad scope regarding use of any neural promoter used to drive expression of a trans-synaptic tracer protein in any

transgenic non-human animal, the Examiner does not find the Applicant's arguments persuasive for the following reasons.

At the time of filing, the art teaches that the isolation of promoters is a lengthy, unpredictable process. The Examiner provided the teachings of Goswami et al. which illustrate the difficulty and unpredictability an artisan faces when characterizing a promoter (First Action, page 6). Goswami et al. teach in deletion analysis that the TGF-β5 promoter has different transcriptional activity, depending on what kind of deletion within the promoter is made. Goswami et al. also teach that there is a difference in promoter activity depending on cell type. Further, there is a difference in promoter activity, depending on the species source of the promoter and on the species in which the promoter is introduced. While the Applicant points the Examiner to specific neural promoters which have activity across species (e.g. the OMP promoter cloned from rats and mice are shown to function in the olfactory in a neuron-specific manner, Applicant's Response, page 11, 4th parag., and that the mouse-derived L7 promoter can express lacZ in rat Purkinje cells, Applicant's Response, page 12, 1st parag.), the art has shown that not all neural promoters work in different species of non-human animals. For example, the art teaches that flies, worms, or starfish do not have a cerebellum. Thus, an artisan would not know how to use the mouse-derived L7 promoter in flies, worms, or starfish. Furthermore, an artisan would not know how to obtain a neuron comprising a transgene construct comprising an L7 promoter from a fly, worm, or starfish and know what functions to test. Conversely, the art teaches that the Drosophila eye is comprised of ommatidia, or an array of about 800 hexagonal units, each of which is composed of a

central core of 8 photorecptors surrounded by pigment cells and lens secreting cone cells (Bowtell, et al., 1989, PNAS, USA, 86: 6245-6249, page 6245, 1st col., 1st parag.). Mammals do not have ommatidia and it would be highly unlikely that the sevenless promoter, which expresses early in ommatidial formation, would have activity in a developing mammalian eye. Therefore, the art does not enable an artisan to practice the claimed invention under the full scope of any non-human transgenic animal comprising any neural-specific promoter.

With regards to the issue of generating transgenic non-human animals using pronuclear microinjection as unreliable, the Examiner raises the issue not because economic feasibility is a problem. Rather, the problems that were being addressed were biological. As taught by Mullins and Mullins (1996), pronuclear injection involves random integration of a transgene. The ramifications of this are 1) the transgene enters a place in the genome wherein it is silenced, 2) the transgene enters a place in the genome where an enhancer influences its expression and the transgene is misexpressed temporally and/or spatially, 3) multiple copies of transgene integrate into the genome, wherein one cannot predict the amount of transgene an non-human animal will produce. In order for one to determine the results of the transgenesis, an artisan would need to characterize the non-human animal. This is supported by Mench (1999, Murray et al., editors, Transgenic Animals in Agriculture, CAB International: 251-268; see page 259, under "Uniqueness of Transgenic Animals"), who states that "because there can be so much variation in the sites of gene insertion, the numbers of gene copies transferred, and gene expression, every transgenic animal produced using

microinjection is (theoretically, at least) unique in terms of its phenotype." Thus, as taught by Mullins and Mullins and Mench, the art teaches that one cannot predict the phenotypes that will be exhibited by the transgenic non-human animals. Each non-human animal would need to be characterized as each non-human animal is unique. For this reason, the specification does not enable an artisan to generate any transgenic non-human animal by pronuclear injection, wherein the transgene integration is random and the phenotype is predictable.

With regards to claims 13-20, wherein the claims are directed to a non-human animal model obtained from a cross of a transgenic non-human animal comprising a transgene comprising a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter and a non-human animal comprising a neurological pathology and a method of using the non-human animal model obtained from the cross in a screen for identifying substances that restore neurological pathways, the specification does not teach an artisan how to use any non-human animal obtained from the cross encompassed within the scope of the claims. The specification, at the time of filing teaches an artisan how to make and use non-human animals that express WGA in Purkinje cells and in olfactory and vomeronasal cells by using the L7 and the OMP promoter. However, the specification does not teach how to use other make and use other neural-specific promoters that express in other neural tissues. This becomes an issue in light of the fact that there are neurological pathologies that involve neurons other than those in the olfactory and the Purkinje cells of the cerebellum. For example, the neurons that are affected in amyotrophic lateral sclerosis (ALS, Lou Gehrig's

Disease) are motor neurons. The specification, at the time of filing, does not teach how to make or use a promoter that expresses specifically in motor neurons. Further, the specification does not teach how to use a mouse obtained from a cross between a mouse comprising a transgene construct comprising a nucleic acid sequence encoding WGA operably linked to L7 or to OMP and a mouse model of ALS. For these reasons, the specification does not enable an artisan to practice the claimed invention for the full scope of the claims.

For the reasons described above, the specification and the art do not provide guidance commensurate with the scope of the claims. Thus, the claimed invention is limited to:

1) a transgenic mouse comprising a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a L7 promoter, wherein said transgenic mouse expresses a trans-synaptic tracer protein in Purkinje cells, and a transgenic mouse comprising a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to an OMP promoter, wherein said transgenic mouse expresses a trans-synaptic tracer protein in the olfactory or vomeronasal nerves,

2) a Purkinje cell, or a cell from the olfactory or vomeronasal nerve obtained from said transgenic mice, wherein the cells express a trans-synaptic tracer protein,

3) a method for using a Purkinje cell, or a cell from the olfactory or vomeronasal nerve in a screen for substances that alters the expression level of the trans-synaptic tracer protein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claimed invention is to a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter, a method for screening substances having an effect upon cultured neurons obtained from said transgenic non-human animal, a cultured neuron obtained from said transgenic non-human animal, a transgenic non-human neural animal model obtained by crossing a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter to a non-human animal model for disease resulting from abnormal neural pathways or with a spontaneously mutated animal model, and a method of using said transgenic non-human neurological animal model in a screen for substances.

Claims 1-4, 6-20 are rejected under 35 U.S.C. 102(b) as being anticipated by PCT/JP99/04439, filed August 18, 1999. The instant application is purportedly a continuing application of 09/763,117, which is a 371 of PCT/JP99/04439, see page 1 of specification. This means that the instant application has the same content as that of

the PCT. Thus, the contents in the PCT anticipate the teachings of the instant application.

This 102 rejection may be withdrawn if the Applicant provides a translation of the PCT and if the Applicant establishes the continuity of this Application.

Claims 1-3, 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshihara et al., (1999, Neuron, 22: 33-41).

The claimed invention is to a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter.

Yoshihara et al. teach how to make two transgene constructs, wherein a nucleic acid sequence encoding plant wheat germ agglutinin (WGA) is operably linked to an L7 promoter or to an OMP promoter. The L7 promoter has been characterized to express in cerebellar Purkinje cell-specific expression, while the OMP promoter has been characterized to express in mature olfactory and vomeronasal sensory neurons. Transgenic mice comprising these constructs were produced (Yoshihara et al., page 34, 2nd col., 2nd parag. to page 38, 1st col., 1st parag.). Yoshihara et al. also teach how to make transgenic Drosophila wherein the GAL4/UAS system was used (Yoshihara, et al., page 38, col. 1, 2nd parag. to col. 2). An Rh1-GAL4 line was used to drive expression of GAL4 in the R1-R6 photoreceptor cells of the retina. Nucleic acid sequence encoding WGA was operably linked to the UAS regulatory region, such that binding of GAL4 to the UAS induced expression of WGA transcript. Thus, Yoshihara et

al. anticipate the claims to a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4, 6, 7, 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshihara et al. (1999, Neuron, 22: 33-41).

The claimed invention is to a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter, a method for screening substances having an effect upon cultured neurons obtained from said transgenic non-human animal, a cultured neuron obtained from said transgenic non-human animal, a transgenic non-human neural animal model obtained by crossing a transgenic non-human animal comprised of a transgenic construct comprised of a nucleic acid sequence encoding a trans-synaptic tracer protein operably linked to a neural specific promoter to a non-human animal model for disease resulting from abnormal neural pathways or with a spontaneously mutated animal model, and a method of using said transgenic non-human neurological animal model in a screen for substances.

Yoshihara et al. teach how to make two transgene constructs, wherein a nucleic acid sequence encoding plant wheat germ agglutinin (WGA) is operably linked to an L7 promoter or to an OMP promoter. The L7 promoter has been characterized to express in cerebellar Purkinje cell-specific expression, while the OMP promoter has been characterized to express in mature olfactory and vomeronasal sensory neurons. Transgenic mice comprising these constructs were produced (Yoshihara et al., page 34, 2nd col., 2nd parag. to page 38, 1st col., 1st parag.). Yoshihara, et al. also teach how to make transgenic Drosophila wherein the GAL4/UAS system was used (Yoshihara, et al., page 38, col. 1, 2nd parag. to col. 2). An Rh1-GAL4 line was used to drive expression of GAL4 in the R1-R6 photoreceptor cells of the retina. Nucleic acid sequence encoding WGA was operably linked to the UAS regulatory region, such that binding of GAL4 to the UAS induced expression of WGA transcript.

Yoshihara et al. also teach the applications with which the transgenic mice could be used. Yoshihara teach that the method developed aids artisans to visualize neural networks, wherein WGA is used to label second-order and third-order neurons (page 39, 2nd col., 2nd parag.). Thus, the technique could be applied to a variety of neurobiological studies on the development, anatomy, and functions of the brain. For example, Yoshihara et al. teach that the development of functional synapses can be analyzed by monitoring WGA appearance in the second order neurons. Yoshihara et al. also teach that WGA transgenic mice can be used to visualize changes of specific neural pathways in various spontaneous and gene-targeted mice. This can be accomplished by crossing transgenic WGA mice and mice comprising a neurological

defect, obtaining the progeny of the cross, and comparing the WGA expression pattern in the mice from the cross with transgenic WGA mice with no neurological defect.

In addition to the teachings of Yoshihara, it is well known in the art to obtain cells from a transgenic non-human animal and to use the cells in identifying agents that effect changes in the cell. In the case of Yoshihara, et al., who teach the method in neuronal cells, it would be obvious to obtain neuronal cells that express the transgene and use them in a screen for agents that modulate the neuron's gene expression, survival, maintenance, dendrite extension, synapse formation, enzymatic activity, and neurotransmitter production. Further, in addition to using the progeny of the transgenic WGA mouse and a mouse comprising a neurological defect to study the differences in WGA expression pattern from a transgenic WGA mouse, the progeny can also be used in screens to identify medicaments that could restore neurological pathways.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make a transgenic mouse comprising a transgene, wherein a nucleic acid sequence encoding WGA is operably linked to a neural promoter, such as L7 or OMP and use the neurons from said transgenic mouse to screen for compounds that change the neuron's gene expression, survival, maintenance, dendrite extension, synapse formation, enzymatic activity, and neurotransmitter production. It would have also been obvious to cross the transgenic mouse with a neurological mouse model, in order to obtain progeny wherein the progeny can be compared with a mouse with no defect, by using WGA as a marker. It

would have also been obvious to use the progeny mouse comprising a neurological defect and WGA transgene in a screen for agents that restore neurological pathways.

There would have been a reasonable expectation of success given the results of Yoshihara et al. for teaching how to make transgenic mice that express WGA in neurons and for providing applications for which the transgenic mice could be used.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER